

### **REMARKS**

Claims 1-10 were previously pending. Applicant herein cancels claims 1-8, amends claims 9 and 10, and adds new claims 11-23. Support for the amendments to claims 9 and 10 can be found, for example, at paragraphs 0025, 0033, 0036, 0038, and 0059 of the application as filed. Support for new claims 11-15 can be found, for example, at paragraph 0026 of the application as filed. Support for new claims 16, 17, and 22 can be found, for example, at paragraph 0035 of the application as filed. Support for new claims 18-20 can be found, for example, at paragraphs 0026-0027 of the application as filed. Support for new claim 21 can be found, for example, at paragraph 0028 of the application as filed. Support for new claim 23 can be found, for example, in claims 9 and 10 as filed and in paragraphs 0025-0027, 0033, 0035, 0036, 0038, 0039, and 0059 of the application as filed.

The specification has been amended to include reference to specific sections within the references incorporated by reference in paragraph 0056, and to omit incorporation by reference in paragraph 0034. The new claims and the amendments to the claims and specification add no new matter. Applicant respectfully requests entry of the amendments and new claims.

### **Objection to the Specification**

The Examiner objected to the specification as allegedly improperly incorporating material by reference on pages 8 (paragraph 0034) and 12 (paragraph 0056).

Applicant respectfully disagrees with the Examiner. Applicant submits that the cited references are properly incorporated by reference because the cited references are readily available to the public and are described with particularity. Nevertheless, Applicant has amended the specification to include a reference to particular portions of the cited references of paragraph 0056. Applicant has also amended the specification to omit the allegedly objectionable incorporation by reference on paragraph 0034. Applicant submits that the disclosures in the references cited on page 8 are well known to those of ordinary skill in the

art. In light of the amendments, Applicant requests that the Examiner withdraw his objection.

**Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description**

The Examiner rejected claims 1-10 as failing to satisfy the written description requirement, asserting that the disclosure fails to provide adequate written description of RNAs disclosed in the application. The Examiner further asserted that the Applicant could not rely on U.S. Patent No. 6,111,086 (the '086 Patent) for protocols for synthesizing polynucleotides, since incorporation by reference of the '086 Patent is allegedly improper.

Applicant canceled claims 1-8 for reasons unrelated to the written description rejections. Applicant submits that the Examiner's rejections of claims 1-8 are rendered moot.

The written description requirement is satisfied when an application describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). An applicant demonstrates possession of a claimed invention by describing the claimed invention with all its limitations. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The Examiner has the burden of presenting evidence or reasons why a person of ordinary skill in the art would not recognize that the written description provides support for the claims. *Revised Interim Guidelines for Examination of Patent Applications Under 35 U.S.C. Sec. 112, Paragraph 1*, 64 FR 71427.

Applicant submits that the Examiner has not met his burden of stating a *prima facie* written description rejection, since he has applied an improper standard. The present claims satisfy the written description requirement because the claimed invention with all its limitations is more than adequately described in the application as filed.

Applicant submits that the Examiner improperly applied a written description

standard applicable to claims for isolated nucleotide sequences to method claims wherein the points of novelty of the method claims are unrelated to any particular target mRNA sequence. The claims are not directed to sequence-specific hairpin RNA molecules, and thus it is apt that the application does not disclose nucleotide sequences for thousands upon thousands of RNAs. The Examiner has not articulated how or why the recited structural limitations of the RNAs of the methods would depend on the identity of the target mRNA.

The present claims are directed to methods of using RNA molecules that comprise specific recited structural features that are independent of any particular target mRNA. Any mRNA can be targeted with the claimed methods, using the appropriately complementary RNA molecules with the specific recited structural features. There is simply no need to list sequences of target mRNAs in this application, nor is there a need to list sequences complementary to the target mRNAs, in order to satisfy the written description requirement. Such a requirement would add nothing toward establishing that the Applicant had possession of the claimed methods for using the RNAs with the specific cited structural features, and thus can serve no purpose in satisfying the written description requirement.

The Examiner's reliance on the *Eli Lilly* case is misplaced. The *Eli Lilly* disclosure rule is inapposite to where claim terms at issue are not new or unknown biological materials that ordinary skilled artisans could easily miscomprehend. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003); *see also, Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1321 (Fed. Cir. 2003) ("the *Lilly* disclosure rule does not require a particular form of disclosure because one of skill could determine from the specification that the inventor possessed the invention at the time of filing"). The structures of the materials recited in the present claims are neither new nor unknown.

The application as filed satisfies the written description requirement because it unambiguously conveys to those of skill in the art that the Applicant was in possession of the claimed invention as of the priority date. The specific recited structural features of the RNAs

of the method claims are more than adequately disclosed in the application as filed: Applicant teaches in the application as filed methods for using over 72 exemplary RNA molecules that permute recited structural limitations in the present claims using lamin A/C as a target mRNA. Appropriately, neither the present claims nor the disclosure limit the claimed invention to any particular target mRNA. Applicant submits that any attempt by the Examiner to limit the claimed invention to a specific target mRNA is inappropriate in light of the fact that individual mRNA sequences have no bearing on the scope of the claimed invention. Applicant teaches in his application that the claimed methods are important independent of the sequence of any particular mRNA, and a person of skill in the art reading the application and present claims would appreciate the importance as well. Simply put, the invention is not a hairpin RNA directed against a lamin A/C mRNA, but a method for targeting mRNA using RNAs comprising specific recited structural features.

Applicants have amended the application to specify that certain portions of the '086 Patent are incorporated by reference. Applicant submits that this amendment overcomes the Examiner's objection to the allegedly improper incorporation by reference. Notwithstanding the amendment specifying portions of the '086 Patent, Applicant refers the Examiner to arguments below establishing that methods for making exemplary RNA molecules comprising linkers such as those of the present claims were well known in the art before the filing date of this application. Accordingly, Applicant submits that the present claims fulfill the written description requirement.

**Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement**

The Examiner rejected claims 1-10 as allegedly failing to comply with the enablement requirement. The Examiner asserted that no starting material or reaction conditions are provided, as so a person of ordinary skill in the art would allegedly need to resort to trial and error with little if any reasonable expectation of success in making and using all useful interfering hairpin RNA.

Applicant has canceled composition claims 1-8, and submits that the claim cancellations render the Examiner's rejections to claims 1-8 moot. Applicant herein amends method claims 9 and 10 to specify certain structural elements of the RNAs, and adds method claims 11 to 23.

To satisfy the enablement requirement, the claimed invention must be enabled so that a person of skill in the art could make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). In determining whether the enablement requirement is satisfied, it is to be noted that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). To state a *prima facie* enablement rejection, an Examiner must establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1999).

Applicant respectfully submits that the Examiner has not properly stated a *prima facie* enablement rejection against the method claims, since the Examiner has improperly required a description of nucleotide sequences of RNAs or target mRNAs in order to distinguish the method claims from the prior art. In this regard, the Examiner is referred to the arguments already made of record above in response to the written description rejections. The Examiner is reminded that the claims recite specific structural features that are target mRNA-independent.

Applicant submits that the Examiner has not provided a reasonable basis to doubt the objective truth of the statements in the specification which teach how carry out the methods of the presently claimed invention. In particular, Applicant submits that the Examiner has

not provided a reasonable basis to doubt the objective truth of the teaching contained in paragraphs 0034 to 0036, 0055 to 0057, and 0062 to 0063 as to making the exemplary RNAs, and paragraphs 0037 to 0039, 0060, 0061, and 0063 as to using the exemplary RNAs, and the Figures. The Examiner has failed to articulate a reason why or how the claimed methods would vary, or require undue experimentation, if applied to target mRNA other than lamin A/C mRNA. Accordingly, Applicant submits that the Examiner's enablement rejections are inappropriate.

Applicant refers the Examiner to the specification, where 72 exemplary RNA molecules were synthesized for 6 specified core sequences with specified linkers (see, for example, paragraphs 0043-0046 of the published application, and Figs. 1-3 indicating the structures of polyether linkers of varying length). The specification clearly indicates that the core sequences were directed against (that is, complementary to) the lamin A/C gene (see paragraph 0061, lines 1-3). Applicant submits that the nucleotide sequence of the lamin A/C gene was well known in the art at the time the application was filed. Lamin A/C mRNA was chosen as a convenient target, but the claimed methods are not limited to a particular target mRNA. Using the exemplary RNA molecules, RNA interference experiments were carried out by transfecting the exemplary RNA molecules comprising specific recited structural features (see, for example, paragraph 0059) and detecting the silencing of the lamin A/C gene by the exemplary RNA molecules (see, for example, paragraph 0061 and Figs. 4 and 5). Accordingly, all aspects of the present claims are fully enabled by the specification as filed.

Applicant respectfully disagrees with the Examiner's arguments that this case is analogous to *Genentech v. Novo Nordisk* ("Genentech"). *Genentech* was decided on strikingly different facts. In *Genentech*, the claims recited a method for making human growth hormone in a fusion protein and cleaving the fusion protein to make the growth hormone. The patentees tried to rely on the level of skill in the art to enable the claim, but at the time of filing the application it was *not* known in the art how to cleave a fusion protein to make growth hormone, *where the cleaving of the fusion protein was the novel aspect of the*

*claim.* In contrast, the novel aspect of the present claims includes methods for using RNAs with specific recited structural features to inhibit target mRNAs. The novel aspects of the claimed invention do not include how to make RNAs with non-nucleotide loops. Methods for making hairpin RNAs with non-nucleotide loops are well known in the art, as reflected by the references cited herein, described below, and provided in the attached information disclosure statement. Thus, *Genentech* sheds no light on any alleged written description or enablement issues with respect to the present claims. *Genentech* is simply inapplicable to the facts of this case.

A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Methods for making hairpin RNAs with non-nucleotide linkers were well known in the art at the time of filing of this application (*i.e.*, the priority date of August 2, 2002). Applicant refers the Examiner to references provided in the enclosed information disclosure statement. For example, U.S. Patent No. 6,111,086 with an issue date of August 29, 2000 (teaching methods for making RNA). Applicant also refers the Examiner to U.S. Patent No. 6,008,400 with an issue date of December 28, 1999 (teaching methods for making RNA), U.S. Patent No. 5,889,136 with an issue date of May 30, 1999 (teaching methods of making RNA), U.S. Patent No. 6,362,323 with an issue date of March 26, 2002 (disclosing methods for making enzymatic RNAs with polyether loops), U.S. Patent No. 6,380,377 with an issue date of April 30, 2002 (disclosing methods for making RNAs with loops having alkylene, polyamine, polyester, polyethylene glycol, and polyalcohol groups for hybridization analysis; see for example col. 10 lines 10-64). Thus, methods for making hairpin RNAs having non-nucleotide linkers were well known in the art before the filing date of the present application. Applicant submits that the present application adequately discloses to a person of ordinary skill in the art how to make and use the claimed invention whether or not the present application discloses such methods in great detail or not.

Accordingly, in light of the amendments and remarks above, Applicant requests reconsideration and withdrawal of the written description and enablement rejections.

**Rejections Under 35 U.S.C. 112, Second Paragraph**

The Examiner rejected claims 1-10 as allegedly indefinite. The Examiner asserted that the term "short" in claims 5-8 renders those claims indefinite. The Examiner asserted that the term is relative and that the specification does not provide a standard for ascertaining the degree, and a person of ordinary skill in the art would not reasonably be apprised of the scope of the claimed invention.

Applicant has canceled claims 1-8. Applicant submits that cancellation of the claims render the Examiner's rejections moot.

The Examiner rejected claims 1-10, alleging that the term "interfering" is indefinite.

Applicant respectfully disagrees with the Examiner. Applicant submits that the meaning of "interfering," when referring to an RNA molecule, is definite to persons of skill in the art. However, in order to expedite prosecution of the claims, Applicant amended the claims to remove the word "interfering," and submits that this amendment renders the Examiner's rejections moot.

The Examiner rejected claim 10 as lacking in antecedent support for "the mRNA," "the gene", and "said double-stranded RNA."

Applicant has amended claim 10 to eliminate the lack of antecedent support. Accordingly, Applicant submits that the Examiner's rejection of claim 10 is rendered moot.

**Rejections Under 35 U.S.C. § 103(a)**

The Examiner rejected claims 1-10 as allegedly obvious over U.S. 6,143,901



(Dervan) in view of Yu et al. (2002) *Proc. Natl. Acad. Sci. USA*, 99/9:6047-6052 (Yu). The Examiner asserted that Dervan discloses hairpin nucleic acids with an  $X_1$ -L- $X_2$  conformation wherein  $X_1$  and  $X_2$  are at least partially complementary and L is a non-nucleotide linker, but does not disclose that the complementary nucleic acids are RNA. The Examiner asserted that Yu discloses RNA interference by expression of short interfering RNA and hairpins. The Examiner asserted that it would have been obvious to modify the method of Dervan and apply it to short interfering hairpin RNA in light of Yu.

Applicant respectfully disagrees with the Examiner. Alone or in combination with any other reference, Dervan does not disclose, teach or suggest a method for inhibiting an mRNA using RNAs with the claimed structural limitations. Rather, Dervan discloses

... novel oligomers for forming high affinity complexes with dsDNA. The oligomers comprise organic cyclic groups joined together by short linkers, which oligomers fit into the minor groove of dsDNA and form complementary base pairs with specific nucleotide base pairs in the dsDNA target sequence.

(Dervan, at col. 3, lines 33-38). In contrast, the invention as presently claimed recites nothing about organic cyclic groups joined by short linkers that fit into dsDNA groove, but instead includes a method for inhibiting an mRNA employing RNAs comprising specific recited features not disclosed in Dervan, including a non-nucleotide loop of 10-24 atoms comprising a polyether, a polyamine, a polyester, a polyphosphodiester, an alkylene, or a combination thereof. Thus, Dervan does not disclose, teach, or suggest the invention as presently claimed. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejections based on the Dervan reference.

Applicant submits that the Yu reference does not disclose, teach, or suggest claimed methods using RNA with the recited structural limitations. Rather, Yu discloses hairpin RNA molecules whose RNA strands are connected by a loop of three nucleotides (see, for example, Yu at page 6049, column 2, lines 10-11). In contrast, the invention as presently

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claimed includes a flexible non-nucleotide loop region of 10 to 24 atoms in length.

Accordingly, Applicant submits that Yu, alone or in combination with Dervan, does not disclose, teach, or suggest the invention as presently claimed. Further, Applicant submits that there is no motivation in Dervan or Yu to combine the references to arrive at the invention as presently claimed. Accordingly, Applicant requests reconsideration and withdrawal of the rejections based on the Yu reference.

### **Conclusion**

In view of the foregoing amendments, and the remarks set forth above, reconsideration and allowance are respectfully solicited.

No fee other than the enclosed fee for a three-month extension of time is believed to be due with respect to the filing of this amendment. If any further fees are due, or an overpayment has been made, please charge, or credit, our Deposit Account No. 11-0171 for such sum.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicant's attorney at the telephone number provided below.

Respectfully submitted,



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